RUDOLPH MATAS MEDICAL LIBRARY
TULANE UNIVERSITY
SCHOOL OF MEDICINE

JUL 12 1940

Modern Concepts of Cardiovascular Disease

Published monthly by the AMERICAN HEART ASSOCIATION

50 WEST 50TH STREET, NEW YORK, N. Y.

DR. JAMES G. CARR, Chicago, *Editor*

DR. GILBERT H. MARQUARDT, Chicago, *Associate Editor*

Vol. IX July, 1940 No. 7

SUBACUTE BACTERIAL ENDOCARDITIS — A CRITICAL REVIEW

Drab years of failure in the treatment of Subacute Bacterial Endocarditis have been brightened in recent months by the employment of new chemical agents the effects of which, if not yet convincingly curative, have nevertheless been definitely promising.

The previous failures led many investigators to speculate on the reasons which prevented immunological and chemical agents from removing the bacteria which lay imbedded in the vegetations, thence feeding the blood stream and maintaining a continuous and killing bacteriemia. The riddle was made more difficult by the fact that the streptococci themselves were practically avirulent for all laboratory animals. This speculation led to attempts to reproduce the disease experimentally, to treat the disease so reproduced, and finally to investigate the character of the bacterial vegetation with a view to determining, if possible, the source of therapeutic failure in human cases.

Although many of the older writers undoubtedly recognized the disease, the first clear description of the bacteriology and its constant importance in diagnosis was that by Schottmueller in 1910. Almost simultaneously Libman described the disease and did more than anyone to place the clinical picture before the eyes of the practising physician. It was not until 1923 that the work of reproducing the disease, begun in the clinic of Dr. Longcope in 1917, was first reported. This work was based on the alleged importance which preceding — usually rheumatic — damage plays in permitting implantation of bacteria. The method employed was to damage the mitral or aortic valve mechanically, and later to produce infection of the injury by intravenous inoculation of non-hemolytic streptococci. It is true that evidence of long standing injury is not always available, and it is possible that some of the cases of acute bacterial endocarditis develop on injuries that are of exceedingly short duration; injuries of the type of simple erosions which probably attend some severe febrile diseases. Nedzel has raised the question of the mechanism of production of such erosions in his work, in which he was able to produce erosive lesions in dogs following injections of pitressin. In a certain number of animals such lesions become infected, with resulting bacterial vegetations. Experimental production of endocarditis without previously infected injury of any kind has been effected in dogs by Blahd, Frank and Saphir, and in rabbits by McNeel, Spence, and Waseen. In the first of these experiments, beta hemolytic streptococci obtained from pneumonia in a dog were used; in the second study, non-hemolytic streptococci were injected frequently over a comparatively long period.

Experience with human subjects yields instances in which infection of the heart valve takes place without known or recognizable preceding damage. Such are the cases of gonococcal endocarditis, and occasional cases of other acute malignant forms. It is impossible in either experimental or the last-mentioned instances of "primary" infection to exclude the possibility of an erosive lesion having preceded the implantation of bacteria, unless one wishes to accept the idea that in some instances the vegetation is produced not by implantation but by thrombosis of the capillaries of the valves. This latter mechanism may operate in the case of gonococcal endocarditis, which occurs frequently on the tricuspid valve which is richly supplied with penetrating capillaries.

Production of endocarditis in dogs with less obvious preceding damage was reported by Friedman, Katz and Howell in 1938. In this work, perforated bakelite capsules containing infected blood agar were inserted into the ventricle, and the subsequent effects noted. Vegetations were produced on those valves that came into contact (Tamponade) with the capsule. The early response to such contact was proliferative. Later "fibrin" deposited and made up most of the vegetation. Supported by studies of the role that fibrin plays in supporting the life of streptococci, Friedman developed the argument that the vegetation encrusted as it is with fibrin, shields the streptococci from the killing action of leucocytes and serum. Immunological and chemical agents have so far failed because they could not gain access to the protected streptococci huddled under the layer of fibrin.

Somewhat opposing this view are the studies by Allen of the microscopic structure of the bacterial vegetation using certain special tissue stains. These studies dispute the idea that the vegetation is a thrombus-mass, and tend to establish the process as one of necrosis of tissue, since collagen fibres can be traced into the vegetation from its base. It is admitted that a layer of implanted fibrin caps the vegetation.

Whatever the importance of fibrin may be in shielding the underlying bacteria from destructive immunological and chemical agents there are two facts encountered in our work which merit consideration in connection with the argument. The first is that bacteria spread apparently by contiguous colonization, along the normal endocardium adjacent to the vegetation, *without* any underlying reaction in the tissues and *without* any covering of fibrin. The second is that cured animals, as long as one year after recovery, showed bacterial masses lying under pink staining material (fibrin?). These organisms were either dead or unable to infect the

blood stream. If such masses contained living bacteria, then it is reasonable to say that bacteriemia is *not* maintained by those streptococci which are imbedded in fibrin, but rather by those which are growing free of fibrin.

If this last viewpoint is sound then fibrin is an important element in the protection of the body against inoculation of the blood stream by endocardial vegetations, but unfortunately it is not deposited quickly enough to stop bacterial extensions.

One of the most interesting observations made by Friedman et al. was that the vegetation once established, persisted, while bacterial implants made in the myocardium, aorta or subcutaneous tissue were rapidly infiltrated with destructive leucocytes and consequently removed. In this connection, it has been reported that infected agar implanted subcutaneously in a patient with subacute bacterial endocarditis, was rapidly neutralized, and found to be inert at autopsy. This reemphasized the original problem of the pathogenesis of the vegetation.

Following their studies of the relation of fibrin to the protection of streptococci in vegetations, Friedman, Hamburger, and Katz reported the use of heparin alone in the treatment of subacute bacterial endocarditis. Heparin was chosen on account of its capacity to prevent clot or thrombus formation. Unfortunately the drug proved toxic in the reported instance of its use. No observations were reported concerning the probable effect of the drug on the deposit of fibrin. At the same time a report was published by Kelson and White on the use of heparin in combination with sulfapyradine. Although it is impossible to draw definite conclusions from this rather limited experience, the authors were sufficiently impressed to urge further study of these drugs in combination.

There are other reports in the recent literature concerning the use of sulfapyridine and sulfanilamide in the treatment of this disease which are not encouraging, although the favorable reports by Fulcher and Scott, and Orgain and Poston, of the curative action of sulfanilamide in the treatment of gonococcal endocarditis are highly important, since they reveal the fact that one form of bacterial endocarditis is curable by chemotherapy and they prompt the belief that subacute streptococcal endocarditis may yet be cured if the proper agent can be found.

In the experimental disease in dogs both merthiolate injected intravenously and sulfanilamide administered orally, were curative in fifty per cent of the animals. Neither of these drugs has been of value to human beings with this disease. But not only is the difference in animal species important, but the human disease is engrafted on an old injury produced by disease while the experimental disease was engrafted on injury produced by trauma. In either case the vegetation consists of a pink staining mass containing clumps of bacteria just underneath the surface; a rather dense zone of leucocytic infiltration beneath the bacterial layer, and a fibroblastic reaction in the deeper structures. That this pink staining material is mostly necrotic tissue is the view of Allen. Certainly the imbedded bacteria are in all stages of involution. What determines the rather constant level at which the bacteriemia is maintained is not clear. By constant level is meant the rather constant colony count which is maintained by a given patient. It does not seem to depend on the amount of bacteria that can be removed from the blood stream per hour as Friedman suggests, since such calculations based on the disappearance time of injected streptococci, in animals, are upset by the fact that the disappearance time, at least in rabbits, is the same irrespective of the size of the inoculated dose.

Whatever the factors at work may be, it is certain that in dogs the blood stream is sterilized and the animals recover and live indefinitely following treatment with merthiolate or sulfanilamide as outlined above. Recently, utilizing the knowledge that bacteria, inoculated intravenously in rabbits, take three to four hours to disappear from the blood, merthiolate was administered to a patient in transfusions lasting six hours. Four such treatments ten days apart were administered. In all 125 c.c. of one per cent solution of merthiolate were used. Seventeen blood cultures were positive. Eleven days after the last treatment the patient died and showed enough evidence of mercurial poisoning of the stomach, colon, and kidneys, to support a diagnosis of death due to poisoning by mercury. But there were no vestiges of bacterial vegetation on the valve.

There are numerous experiences reported with the use of sulfapyridine showing that the drug brings about a sterilization of blood culture even if it cannot be said that the blood is sterilized. This distinction is important. Nevertheless, in spite of the deficiencies in the present situation, we are getting into an attitude of hopeful expectancy with regard to finding a cure of this hitherto unconquerable disease.

In conclusion we may summarize our understanding of the question by stating that subacute bacterial endocarditis is a vegetative lesion of the valves and neighboring endocardial surfaces caused in most instances by the implantation of streptococci on sites of previous injury. This injury is usually rheumatic in origin, although it may occasionally be syphilitic and sometimes congenital. Other bacteria may be found in the subacute disease. The disease has been reproduced and cured in dogs. Recent studies have emphasized the importance of fibrin in preventing drugs and immunological agents from reaching the imbedded streptococci. Most recent therapeutic efforts have taken this view of the importance of fibrin into consideration and have included the use of heparin alone, or with sulfapyridine.

Even though the hypothesis concerning the role of fibrin be defective the therapeutic results referred to are promising. The future looks brighter.

Ralph A. Kinsella, M. D.
St. Louis, Mo.